IN RE APPLICATION OF	:	**INFECTIO RECHERCHE INC. ET AL.,**
FOR	:	SYSTEM FOR CHARGE-BASED DETECTION OF NUCLEIC ACIDS
NO.	:	PCT/CA2004/002118
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INTERNATIONAL PATENT CLASSIFICATION (IPC)	:	C12Q 1/68
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Montreal, Quebec, Canada
October 12, 2005

AMENDMENTS UNDER ARTICLE 34

International Preliminary Examining Authority
Canadian Intellectual Property Office
Place du Portage I, C114-1st floor, Box PCT
50 Victoria street
Gatineau, Quebec K1A 0C9

Dear Sir:

The present is in response to the Written Opinion of the International Searching Authority dated April 21, 2005 and is accompanied, by separate letter, with a Demand under Article 31 of the Patent Cooperation Treaty.

Please modify the above mentioned patent application as follows;

IN THE CLAIMS

Please replace present claim pages 38- 42 with new claim pages 38- 42 and insert new claim pages 43 and 44. New claim pages 38-44 are submitted herewith.

REMARKS

The Applicant hereby takes the opportunity to correct a typographical error in the numbering of the claims starting at claim 24 (1st). The Applicant has therefore attributed number 24 to old claim 24 (1st), number 25 to old claim 24 (2nd), number 26 to old claim 25 and so on. The dependency of the claims has been modified accordingly. The Applicant has provided a marked-up copy of the claim pages with additions illustrated by underlined text and deletion illustrated with strikethrough.

Additionally, the Applicant has introduced new claims 60 to 71. Support for new independent claims 60 and 64 may be found in claims 1 and 27 (now claim 28), respectively. Support for new independent claim 68 may be found for example in claim 53 (now claim 54). Support for new claims 61, 65 and 69 may be found, for example, in present claim 23. Support for new claims 62, 66 and 70 may be found, for example, in present claim 24. Support for new claims 63, 67 and 71 may be found, for example, in present claim 3. More particularly, support for the expression "unlabeled" may be found, for example, at paragraph 0051 line 34 of the present application.

Objections based on lack of Novelty

The Examiner has objected to present claims 1, 2, 13, 17-19, 23, 24 (1st), 26-28, 39, 43, 44, 48, 49 and 52-54 on the ground that the subject matter of these claims is not novel in light of D1, D2, D3, or D4.

Objections in light of D1

The Applicant respectfully submits that D1 does not anticipate the invention claimed in independent claim 1, claim 27 (now claim 28) nor claim 53 (now claim 54).

D1 does not teach or suggest a method comprising all of the steps of independent claims 1, or 27 (now claim 28).

D1 merely mentions detection methods using conductive polymers (e.g., polythiophene) which are attached to a probe (e.g. PNA) (see paragraph 0058).

Moreover, D1 does not teach or suggest "submitting a negatively charged hybrid to positively charged reporters…capable of electrostatically binding to said hybrids". For example, as the conductive polymer and probe are attached to each other in D1, there is

no step of submitting the hybrid to a reporter. Furthermore, the conductive polymer of D1 are "long carbon-based chains composed of simple repeating units" and have backbone with "alternating single and double bond" (see paragraph 0063). The conductive polymer of D1 does not correspond to the "positively charged reporters selected from group consisting of transition metal atoms, molecules, and macromolecules being capable of electrostatically binding to ....negatively charged capture probe-nucleic acid target hybrids" as claimed in independent claims 1 and 27 (now claim 28).

Finally, D1 does not teach or suggest "a kit comprising a) uncomplexed neutral capture probes, b) a control sample and c) positively charged reporters selected from the group consisting of transition metal cations, molecules or macromolecules; said reporters being capable of electrostatically binding to negatively charged capture probe-nucleic acid target hybrids" as claimed in claim 53 (now claim 54).

In light of the above the Applicant respectfully submits that independent claims 1, 27 (now claim 28) and 53 (now claim 54) as well as claims dependent therefrom (i.e., present claims 2-27, 29-53) and new claims 60-71 are patentably distinct from the teachings of D1.

Objections in light of D2

The Applicant respectfully submits that D2 does not anticipate the invention claimed in independent claim 1, claim 27 (now claim 28) nor claim 53 (now claim 54).

D2 does not teach or suggest a method comprising all of the steps of independent claims 1, or 27 (now claim 28). For example, there is no teaching or suggestion in D2 of "submitting a negatively charged hybrid to positively charged reporters...capable of electrostatically binding to said hybrids".

D2 discusses multimeric nucleic acid comprising repeating units of two or more smaller monomeric molecules. Although D2 mentions that the monomeric unit (of the multimeric biopolymer) may be a peptide nucleic acid, D2 only discusses the use of aptamers which are "selected from random sequence oligonucleotide libraries" (see paragraph 0043 of D2). D2 does not teach or suggest using "nucleic acids targets to bind specifically to complementary neutral capture probes".

Moreover, the redox polymer of D2 is not used for detection purposes. Paragraph 55 clearly mentions that "the redox polymer....can reverse the changes that occurred in the multimeric biopolymer, by analyte binding" and "...the redox polymer override this process". Evidence of the redox polymer being used for reversing the reaction which results from binding of the analyte to the multimeric biopolymer is also found in claim 32 of D2. Therefore, D2 teaches away from the invention as claimed in independent claims 1, 27 (now claim 28) as D2 destroys the complex formed by the target/probe complex.

Additionally, D2 does not teach or suggest "a kit comprising a) uncomplexed neutral capture probes, b) a control sample and c) positively charged reporters selected from the group consisting of transition metal cations, molecules or macromolecules; said reporters being capable of electrostatically binding to negatively charged capture probe-nucleic acid target hybrids" as claimed in claim 53 (now claim 54).

In light of the above the Applicant respectfully submits that independent claims 1, 27 (now claim 28) and 53 (now claim 54) as well as claims dependent therefrom (i.e., present claims 2-27, 29-53) and new claims 60-71 are patentably distinct from the teachings of D2.

Objections in light of D3

The Applicant respectfully submits that D3 does not anticipate the invention claimed in independent claim 1, claim 27 (now claim 28) nor claim 53 (now claim 54).

D3 does not teach or suggest a method comprising all of the steps of independent claims 1, or 27 (now claim 28).

For example, there is no teaching or suggestion in D3 of a "higher order complex" formed by target, probe (negatively charged hybrid) and reporter. In fact, D3 teaches away from the present invention, as detection is obtained by dissociation of the complex (see Fig. 1a of D3).

Additionnally there is no teaching or suggestion in D3 of "submitting a negatively charged hybrid to positively charged reporters...capable of electrostatically binding to said hybrids". For example, as the recognition element and the polymer of the biosensor

are attached to each other in D3, there is no step of submitting the hybrid to a reporter. Moreover, D3 does not teach or suggest "negatively charged capture probe-nucleic acid target hybrids".

In addition, D3 does not teach or suggest a kit comprising "a) uncomplexed neutral capture probes, b) a control sample and c) positively charged reporters selected from the group consisting of transition metal cations, molecules or macromolecules; said reporters being capable of electrostatically binding to negatively charged capture probe-nucleic acid target hybrids" as claimed in claim 53 (now claim 54).

In light of the above the Applicant respectfully submits that independent claims 1, 27 (now claim 28) and 53 (now claim 54) as well as claims dependent therefrom (i.e., present claims 2-27, 29-53) and new claims 60-71 are patentably distinct from the teachings of D3.

Objections in light of D4

The Applicant respectfully submits that D4 does not anticipate the invention claimed in independent claim 1, claim 27 (now claim 28) nor claim 53 (now claim 54).

D4 does not teach or suggest a method comprising all of the steps of independent claims 1, or 27 (now claim 28).

For example, D4 does not teach or suggest "neutral capture probe". Furthermore, the electrically conductive polymer (e.g.,polythiophene) of D4 is used as a binding support and not for detection purposes. Additionally, D4 does not teach or suggest method of detecting nucleic acids using "positively charged reporter molecule" nor "negatively charged hybrid".

Moreover, D4 does not teach or suggest a kit comprising "a) uncomplexed neutral capture probes, b) a control sample and c) positively charged reporters selected from the group consisting of transition metal cations, molecules or macromolecules; said reporters being capable of electrostatically binding to negatively charged capture probe-nucleic acid target hybrids" as claimed in claim 53 (now claim 54).

In light of the above the Applicant respectfully submits that independent claims 1, 27 (now claim 28) and 53 (now claim 54) as well as claims dependent therefrom (i.e., present claims 2-27, 29-53) and new claims 60-71 are patentably distinct from the teachings of D4.

Objections in light of D5

The Examiner has objected to claim 24 2nd (now claim 25) on the ground that the subject matter of theis claim is not novel in light of D5.

Applicant respectfully submits that D5 does not anticipate the invention claimed in claim 24 2nd (now claim 25) which is dependent on claim 1. More particularly, D5 does not teach or suggest a method comprising all of the steps of claim 24 2nd (now claim 25).

For example, D5 does not teach or suggest a method using "positively charged reporters selected from group consisting of transition metal atoms, molecules, and macromolecules being capable of electrostatically binding to said hybrids" which comprises "an enzyme".

In light of the above the Applicant respectfully submits that claim 24 2nd is patentably distinct from the teachings of D5.

Objections based on lack of Inventive step

The Examiner has objected to claims 1, 2, 13, 17-19, 23, 24(1st), 26-28, 39, 43, 44, 48, 49 and 52-54 as lacking an inventive step in light of the teachings of D6 in combination with D9 or D10.

D6 describes the use of zwitterionic polythiophene for binding to positively or negatively charged polypeptide. D6 does not teach or suggest the use of polythiophene for binding to negatively charged hybrid made of a neutral capture probe and a complementary nucleic acid target.

D9 and D10 describe various utilities for PNA. Neither D9 nor D10 teach or suggest the use of positively charged reporter (such as a polythiophene) for binding to negatively charged hybrid made of a neutral capture probe and a complementary nucleic acid target.

The Applicant respectfully submits that neither D6, D9 nor D10 taken alone or in combination teach or suggest a method of detection using a positively charged reporter (such as a polythiophene) capable of electrostatically binding a negatively charged hybrid made of a neutral capture probe and a complementary nucleic acid target as claimed in independent claims 1, 27 (now claim 28). In addition, neither D6, D9 nor D10 taken alone or in combination, teach or suggest a "higher order complex" formed by nucleic acid target/probe (i.e, negatively charged hybrid) and reporter.

Furthermore, the Applicant respectfully submits that neither D6, D9 nor D10 taken alone or in combination teach or suggest a kit comprising "a) uncomplexed neutral capture probes, b) a control sample and c) positively charged reporters selected from the group consisting of transition metal cations, molecules or macromolecules; said reporters being capable of electrostatically binding to negatively charged capture probe-nucleic acid target hybrids" as claimed in claim 53 (now claim 54).

In light of the above the Applicant respectfully submits that independent claims 1, 27 (now claim 28) and 53 (now claim 54) as well as claims dependent therefrom (i.e., present claims 2-27, 29-53) and new claims 60-71 are patentably distinct from the teachings of D6, D9 and D10 either taken alone or in combination.

The Examiner has further objected to claims 1, 2, 13, 17-19, 23, 24(1^{st}), 26-28, 39, 43, 44, 48, 49 and 52-54 as lacking an inventive step in light of the teachings of D7 or D8 in combination with D9 or D10.

The Examiner contends that it would have been obvious for a person skilled in the art to substitute the DNA probes of D7 or D8 with the peptide nucleic acid probes of D9 or D10.

D8 clearly specifies that the polymers have high affinity for negatively charged molecules. Evicence of such affinity is exemplified in D8 by a color appearing when a polythiophene polymer and a single stranded (or denatured double-stranded) DNA molecule are mixed (e.g., see Example 7). Therefore, background signal occurs between the polymer and the DNA probe when one uses the teachings of D8, i.e., the formation of a polymer/DNA probe complex may result in a falsely positive reaction which significantly reduces the performance of the method of D8. This problem has not been recognized in D8. In contrast, the present

application clearly specifies that the polythiophenes do not bind to the neutral capture probes and therefore avoids such problem. Additionally, the Applicant respectfully submits that there is no teaching or suggestion in D8 of a method or kit which advantageously uses neutral capture probe for solving the problem of undesirable background signal associated with the binding between negatively charged probe and positively charged polymer.

The Applicant respectfully submits that simply substituting the DNA probes of D8 with the peptide nucleic acid probes of D9 or D10 would not succesfully lead to the present invention as D8 does not teach the method of the present invention. For example, D8 does not teach or suggest "uncomplexed neutral probe" as claimed herein. To the contrary, D8 relies on either a) a color change occurring when the target is added to a probe complexed with polymer, or b) the appearance of a fluorescent signal when target is added to a probe complexed with polymer. Alternatively, D8 teaches electrochemical detection which relies on the use of a probe having a negative charge.

In light of the above, the Applicant respectfully submits that there is no expectation of success in simply substituting the DNA probe of D8 with the peptide nucleic acid probes of D9 or D10.

D7 teaches the use of zwitterionic polythiophenes for binding single-stranded or double-stranded DNA. As it is the case for D8, D7 teaches the use of polymers with DNA probes resulting in more background signal. There is no teaching or suggestion in D7 of a method or kit which advantageously uses neutral capture probe for solving the problem of undesirable background signal associated with negatively charged probe and positively charged reporter of the present invention.

D9 and/or D10 generally discuss the uses of PNA. Neither D9 and/or D10 discusses the uses of PNA in conjunction with the positively charged reporter or the present invention for efficiently solving the above mentioned problems. Additionally, neither D9 and/or D10 teach or suggest the method or kit of the present invention. Therefore, the teachings of D9 and/or D10 does not cure the deficiency of neither D8 nor D7.

In light of the above the Applicant respectfully submits that independent claims 1, 27 (now claim 28) and 53 (now claim 54) as well as claims dependent therefrom (i.e., present claims 2-27, 29-53) and new claim 60-71 are patentably distinct from the

teachings of D7, D8, D9 and D10 either taken alone or in combination.

The Examiner has also objected to claims 3-12, 14-16, 20-22, 25, 29-38, 40-42, 45-47, 51 and 55-57 as lacking an inventive step having regard to D1, D2, D3, D4 or D5 in combination with common general knowledge.

As indicated above, the Applicant respectfully submits that neither D1, D2, D3 or D4 teach or suggest the invention of independent claims 1, 27 (now claim 28) or 53 (now claim 54) as well as of claims dependent therefrom (i.e., present claims 2-27, 29-53) and that D5 does not teach or suggest the invention claimed in claim 24 2nd.

Therefore, the Applicant respectfully submits that claims 3-12, 14-16, 20-22, 25, 29-38, 40-42, 45-47, 51 and 55-57 are patentably distinct from the teachings of D1, D2, D3, D4 or D5 either taken alone or in combination or in view of the common general knowledge.

The status of the claims and support for amendments to the claims may be summarized as follows;

Claim No.	
1-24 (1st)	Unchanged
24(2nd) – 58	Renumbered as 25-59- Dependency modified to renumbering of claims
60-71	New

Accordingly, in light of the above remarks the Applicant respectfully requests favourable reconsideration with respect to the above identified application.

INFECTIO RECHERCHE INC. ET AL.,

By their patent agents

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Encl. New claim pages 38-44 (marked up copy and clean copy)

comprise polythiophenes.

24. A method according to claim 23, wherein said polythiophenes are water soluble and cationic.

25. A method according to claim 1, wherein said reporters comprise enzymes.

26. A method according to claim 25, wherein said enzymes comprise alkaline phosphatase having polystyrene beads conjugated thereto.

27. A method according to claim 1, wherein said detection is selected from the group consisting of optical detection, fluorometric detection, colorimetric detection, electrochemical detection, chemiluminescent detection, microscopy and spectrophotometric detection.

28. A method for detecting the presence of nucleic acids in a sample, said method comprising:

(a) exposing uncomplexed neutral capture probes to a sample possibly containing complementary nucleic acid targets and containing positively charged reporters selected from group consisting of transition metal atoms, molecules and macromolecules, thereby generating a mixture;

(b) submitting said mixture to hybridization conditions which provide for said nucleic acids targets to bind specifically to complementary neutral capture probes, thereby generating negatively charged capture probe-nucleic acid target hybrids, said reporters being capable of electrostatically binding to said hybrids, thereby generating higher-order complexes; and

(c) detecting said higher-order complexes.

29. A method according to claim 28, wherein said nucleic acids targets are unlabeled.

30. A method according to claim 1, wherein said capture probes are immobilized on a support surface.

31. A method according to claim 30, wherein said support surface is selected from the group consisting of a glass surface, a silicon surface, a gold surface, an electrode surface, a particle surface, a gel matrix, a membrane surface, a paper surface and a plastic surface.

32. A method according to claim 30, wherein said support surface comprises a solid support surface

33. A method according to claim 32, wherein said solid support surface comprises a probe array.

34. A method according to claim 30, wherein said neutral capture probes are chemically modified to incorporate a functional group providing for said probes to covalently link to said support surface.

35. A method according to claim 34, wherein said functional group is selected from the group consisting of amine, aldehyde, thiol, epoxy or carboxyl moieties.

36. A method according to claim 30, wherein said support surface is coated with a passivation agent preventing non-specific binding of nucleic acid targets.

37. A method according to claim 36, wherein said passivation agent is selected from the group consisting of polyvinylpyrollidone, polyethylene glycol, and BSA.

38. A method according to claim 30, wherein said support surface is chemically modified, to facilitate coupling and chemical bonding of said neutral probe to said support surface.

39. A method according to claim 38, wherein said support

surface is chemically modified to contain functional groups selected from the group consisting of an aldehyde, an aminoalkylsilane activated with carbonyldiimidazole, thiol, epoxy or carboxyl moieties.

40. A method according to claim 28, wherein said neutral capture probes are selected from the group consisting of peptide nucleic acids (PNA), and methylphosphonate.

41. A method according to claim 28, wherein said nucleic acid targets are selected from the group consisting of DNA and RNA molecules.

42. A method according to claim 28, wherein said nucleic acid targets are generated by methods selected from the group consisting of polymerase chain reaction (PCR), reverse transcriptase-PCR (RT-PCR), strand displacement amplification (SDA), ligase chain reaction (LCR), transcription-associated amplification, nucleic acid sequence-based amplification (NASBA), whole genome amplification (WGA), helicase-dependent isothermal amplification, and chemical synthesis.

43. A method according to claim 28, further comprising a washing step after step (b).

44. A method according to claim 28, wherein said reporters exhibit low affinity for uncharged probes

45. A method according to claim 28, wherein said reporters are capable of electrostatically binding to the phosphate backbone of said hybrids.

46. A method according to claim 28, wherein said transition metal atoms are selected from the group consisting of Ag^{+} and Cd^{++}.

47. A method according to claim 28, wherein said transition metal atoms comprise ions that can be chemically modified to yield higher-order complexes using bound nucleic acids as a scaffold.

48. A method according to claim 28, wherein said detection includes a chemical reaction step rendering said transition metal cations detectable.

49. A method according to claim 28, wherein said reporters comprise polythiophenes.

50. A method according to claim 49, wherein said polythiophenes are water-soluble and cationic.

51. A method according to claim 28, wherein said reporters comprise enzymes.

52. A method according to claim 51, wherein said enzymes comprise alkaline phosphatase having polystyrene beads conjugated thereto.

53. A method according to claim 28, wherein said detection is selected from the group consisting of optical detection, fluorometric detection, colorimetric detection, electrochemical detection, chemiluminescent detection microscopy and spectrophotometric detection.

54. A kit for detecting the presence of nucleic acids in a sample, said kit comprising:

uncomplexed neutral capture probes;

a control sample possibly containing nucleic acid targets that are complementary to the neutral capture probes; and

one or more positively charged reporters selected from the group consisting of transition metal cations, molecules or macromolecules; said reporters being capable of electrostatically binding to negatively charged capture probe-nucleic acid target hybrids.

55. A kit according to claim 54, wherein said neutral capture probes are selected from the group consisting of peptide nucleic acids (PNA) and methylphosphonate.

56. A kit according to claim 54, wherein said capture probes are immobilized on a support surface.

57. A kit according to claim 56, wherein said support surface is selected from the group consisting of a glass surface, a silicon surface, a gold surface, an electrode surface, a particle surface, a gel matrix, a membrane surface, a paper surface or a plastic surface.

58. A kit according to claim 56, wherein said support surface comprises a solid support surface support

59. A kit according to claim 58, wherein said solid support surface comprises a probe array.

60. A method for detecting the presence of nucleic acids in a sample, said method comprising:

(a) exposing uncomplexed and unlabeled neutral capture probes to a sample possibly containing unlabeled complementary nucleic acid targets, thereby generating a mixture;

(b) submitting said mixture to hybridization conditions which provide for said nucleic acids targets to bind specifically to complementary neutral capture probes, thereby generating negatively charged capture probe-nucleic acid target hybrids;

(c) adding said negatively charged hybrids to positively charged reporters selected from group consisting of transition metal atoms, molecules, and macromolecules being capable of electrostatically binding to said hybrids, thereby generating higher-order complexes; and

(d) detecting said higher-order complexes.

61. The method of claim 60, wherein said positively

charged reporter comprises a polythiophene.

62. The method of claim 61, wherein said polythiophene is a positively-charged water-soluble polythiophene derivative.

63. The method of claim 60, wherein said neutral capture probes are immobilized at the surface of a solid support.

64. A method for detecting the presence of nucleic acids in a sample, said method comprising:

(a) exposing uncomplexed and unlabeled neutral capture probes to a sample possibly containing unlabeled complementary nucleic acid targets and containing positively charged reporters selected from group consisting of transition metal atoms, molecules and macromolecules, thereby generating a mixture;

(b) submitting said mixture to hybridization conditions which provide for said nucleic acids targets to bind specifically to complementary neutral capture probes, thereby generating negatively charged capture probe-nucleic acid target hybrids, said reporters being capable of electrostatically binding to said hybrids, thereby generating higher-order complexes; and

(c) detecting said higher-order complexes

65. The method of claim 64, wherein said positively charged reporter comprises a polythiophene.

66. The method of claim 65, wherein said polythiophene is a positively-charged water-soluble polythiophene derivative.

67. The method of claim 64, wherein said neutral capture probes are immobilized at the surface of a solid support.

68. A kit for detecting the presence of nucleic acids in a sample, said kit comprising:

uncomplexed and unlabeled neutral capture probes;

a control sample possibly containing unlabeled nucleic acid targets that are complementary to the neutral capture probes; and

one or more positively charged reporters selected from the group consisting of transition metal cations, molecules or macromolecules; said reporters being capable of electrostatically binding to negatively charged capture probe-nucleic acid target hybrids.

69. The kit of claim 68, wherein said positively charged reporter comprises a polythiophene.

70. The kit of claim 69, wherein said polythiophene is a positively-charged water-soluble polythiophene derivative.

71. The kit of claim 68, wherein said neutral capture probes are immobilized at the surface of a solid support.

comprise polythiophenes.

24. A method according to claim 23, wherein said polythiophenes are water soluble and cationic.

~~24~~ 25. A method according to claim 1, wherein said reporters comprise enzymes.

~~25~~ 26. A method according to claim 25 ~~claim 24~~, wherein said enzymes comprise alkaline phosphatase having polystyrene beads conjugated thereto.

~~26~~ 27. A method according to claim 1, wherein said detection is selected from the group consisting of optical detection, fluorometric detection, colorimetric detection, electrochemical detection, chemiluminescent detection, microscopy and spectrophotometric detection.

~~27~~ 28. A method for detecting the presence of nucleic acids in a sample, said method comprising:

(a) exposing uncomplexed neutral capture probes to a sample possibly containing complementary nucleic acid targets and containing positively charged reporters selected from group consisting of transition metal atoms, molecules and macromolecules, thereby generating a mixture;

(b) submitting said mixture to hybridization conditions which provide for said nucleic acids targets to bind specifically to complementary neutral capture probes, thereby generating negatively charged capture probe-nucleic acid target hybrids, said reporters being capable of electrostatically binding to said hybrids, thereby generating higher-order complexes; and

(c) detecting said higher-order complexes.

comprise polythiophenes.

24. A method according to claim 23, wherein said polythiophenes are water soluble and cationic.

~~24~~ 25. A method according to claim 1, wherein said reporters comprise enzymes.

~~25~~ 26. A method according to claim 25 ~~claim 24~~, wherein said enzymes comprise alkaline phosphatase having polystyrene beads conjugated thereto.

~~26~~ 27. A method according to claim 1, wherein said detection is selected from the group consisting of optical detection, fluorometric detection, colorimetric detection, electrochemical detection, chemiluminescent detection, microscopy and spectrophotometric detection.

~~27~~ 28. A method for detecting the presence of nucleic acids in a sample, said method comprising:

(a) exposing uncomplexed neutral capture probes to a sample possibly containing complementary nucleic acid targets and containing positively charged reporters selected from group consisting of transition metal atoms, molecules and macromolecules, thereby generating a mixture;

(b) submitting said mixture to hybridization conditions which provide for said nucleic acids targets to bind specifically to complementary neutral capture probes, thereby generating negatively charged capture probe-nucleic acid target hybrids, said reporters being capable of electrostatically binding to said hybrids, thereby generating higher-order complexes; and

(c) detecting said higher-order complexes.

~~28~~ 29. A method according to claim 28 ~~claim 27~~, wherein said nucleic acids targets are unlabeled.

~~29~~ 30. A method according to claim 1, wherein said capture probes are immobilized on a support surface.

~~30~~ 31. A method according to claim 30 ~~claim 29~~, wherein said support surface is selected from the group consisting of a glass surface, a silicon surface, a gold surface, an electrode surface, a particle surface, a gel matrix, a membrane surface, a paper surface and a plastic surface.

~~31~~ 32. A method according to claim 30 ~~claim 29~~, wherein said support surface comprises a solid support surface

~~32~~ 33. A method according to claim 32 ~~claim 31~~, wherein said solid support surface comprises a probe array.

~~33~~ 34. A method according to claim 30 ~~claim 29~~, wherein said neutral capture probes are chemically modified to incorporate a functional group providing for said probes to covalently link to said support surface.

~~34~~ 35. A method according to claim 34 ~~claim 33~~, wherein said functional group is selected from the group consisting of amine, aldehyde, thiol, epoxy or carboxyl moieties.

~~35~~ 36. A method according to claim 30 ~~claim 29~~, wherein said support surface is coated with a passivation agent preventing non-specific binding of nucleic acid targets.

~~36~~ 37. A method according to claim 36 ~~claim 35~~, wherein said passivation agent is selected from the group consisting of polyvinylpyrollidone, polyethylene glycol, and BSA.

~~37~~ 38. A method according to claim 30 ~~claim 29~~, wherein said support surface is chemically modified, to facilitate coupling and chemical bonding of said neutral probe to said support surface.

~~38~~ 39. A method according to claim 38 ~~claim 37~~, wherein

said support surface is chemically modified to contain functional groups selected from the group consisting of an aldehyde, an aminoalkylsilane activated with carbonyldiimidazole, thiol, epoxy or carboxyl moieties.

~~39~~ 40. A method according to claim 28 ~~claim 27~~, wherein said neutral capture probes are selected from the group consisting of peptide nucleic acids (PNA), and methylphosphonate.

~~40~~ 41. A method according to claim 28 ~~claim 27~~, wherein said nucleic acid targets are selected from the group consisting of DNA and RNA molecules.

~~41~~ 42. A method according to claim 28 ~~claim 27~~, wherein said nucleic acid targets are generated by methods selected from the group consisting of polymerase chain reaction (PCR), reverse transcriptase-PCR (RT-PCR), strand displacement amplification (SDA), ligase chain reaction (LCR), transcription-associated amplification, nucleic acid sequence-based amplification (NASBA), whole genome amplification (WGA), helicase-dependent isothermal amplification, and chemical synthesis.

~~42~~ 43. A method according to claim 28 ~~claim 27~~, further comprising a washing step after step (b).

~~43~~ 44. A method according to claim 28 ~~claim 27~~, wherein said reporters exhibit low affinity for uncharged probes

~~44~~ 45. A method according to claim 28 ~~claim 27~~, wherein said reporters are capable of electrostatically binding to the phosphate backbone of said hybrids.

~~45~~ 46. A method according to claim 28 ~~claim 27~~, wherein said transition metal atoms are selected from the group consisting of Ag^{+} and Cd^{++}.

~~46~~ 47. A method according to claim 28 ~~claim 27~~, wherein said transition metal atoms comprise ions that can be chemically modified to yield higher-order complexes using bound nucleic acids as a scaffold.

~~47~~ 48. A method according to claim 28 ~~claim 27~~, wherein said detection includes a chemical reaction step rendering said transition metal cations detectable.

~~48~~ 49. A method according to claim 28 ~~claim 27~~, wherein said reporters comprise polythiophenes.

~~49~~ 50. A method according to claim 49 ~~claim 48~~, wherein said polythiophenes are water-soluble and cationic.

~~50~~ 51. A method according to claim 28 ~~claim 27~~, wherein said reporters comprise enzymes.

~~51~~ 52. A method according to claim 51, wherein said enzymes comprise alkaline phosphatase having polystyrene beads conjugated thereto.

~~52~~ 53. A method according to claim 28 ~~claim 27~~, wherein said detection is selected from the group consisting of optical detection, fluorometric detection, colorimetric detection, electrochemical detection, chemiluminescent detection microscopy and spectrophotometric detection.

~~53~~ 54. A kit for detecting the presence of nucleic acids in a sample, said kit comprising:

uncomplexed neutral capture probes;

a control sample possibly containing nucleic acid targets that are complementary to the neutral capture probes; and

one or more positively charged reporters selected from the group consisting of transition metal cations, molecules or macromolecules; said reporters being capable of electrostatically binding to negatively charged capture probe-nucleic acid target hybrids.

~~54~~ 55. A kit according to claim 54 ~~claim 53~~, wherein said neutral capture probes are selected from the group consisting of peptide nucleic acids (PNA) and methylphosphonate.

~~55~~ 56. A kit according to claim 54 ~~claim 53~~, wherein said capture probes are immobilized on a support surface.

~~56~~ 57. A kit according to claim 56 ~~claim 55~~, wherein said support surface is selected from the group consisting of a glass surface, a silicon surface, a gold surface, an electrode surface, a particle surface, a gel matrix, a membrane surface, a paper surface or a plastic surface.

~~57,~~ 58. A kit according to claim 56 ~~claim 55~~, wherein said support surface comprises a solid support surface support

~~58~~ 59. A kit according to claim 58 ~~claim 57~~, wherein said solid support surface comprises a probe array.

60. A method for detecting the presence of nucleic acids in a sample, said method comprising:

(a) exposing uncomplexed and unlabeled neutral capture probes to a sample possibly containing complementary unlabeled nucleic acid targets, thereby generating a mixture;

(b) submitting said mixture to hybridization conditions which provide for said nucleic acids targets to bind specifically to complementary neutral capture probes, thereby generating negatively charged capture probe-nucleic acid target hybrids;

(c) adding said negatively charged hybrids to positively charged reporters selected from group consisting of transition metal atoms, molecules, and macromolecules being capable of electrostatically binding to said hybrids, thereby generating higher-order complexes; and

(d) detecting said higher-order complexes.

61. The method of claim 60, wherein said positively

charged reporter comprises a polythiophene.

62. The method of claim 61, wherein said polythiophene is a positively-charged water-soluble polythiophene derivative.

63. The method of claim 60, wherein said neutral capture probes are immobilized at the surface of a solid support.

64. A method for detecting the presence of nucleic acids in a sample, said method comprising:

(a) exposing uncomplexed and unlabeled neutral capture probes to a sample possibly containing unlabeled complementary nucleic acid targets and containing positively charged reporters selected from group consisting of transition metal atoms, molecules and macromolecules, thereby generating a mixture;

(b) submitting said mixture to hybridization conditions which provide for said nucleic acids targets to bind specifically to complementary neutral capture probes, thereby generating negatively charged capture probe-nucleic acid target hybrids, said reporters being capable of electrostatically binding to said hybrids, thereby generating higher-order complexes; and

(c) detecting said higher-order complexes

65. The method of claim 64, wherein said positively charged reporter comprises a polythiophene.

66. The method of claim 65, wherein said polythiophene is a positively-charged water-soluble polythiophene derivative.

67. The method of claim 64, wherein said neutral capture probes are immobilized at the surface of a solid support.

68. A kit for detecting the presence of nucleic acids in a sample, said kit comprising:

uncomplexed and unlabeled neutral capture probes;

a control sample possibly containing unlabeled nucleic acid targets that are complementary to the neutral capture probes; and

one or more positively charged reporters selected from the group consisting of transition metal cations, molecules or macromolecules; said reporters being capable of electrostatically binding to negatively charged capture probe-nucleic acid target hybrids.

69. The kit of claim 68, wherein said positively charged reporter comprises a polythiophene.

70. The kit of claim 69, wherein said polythiophene is a positively-charged water-soluble polythiophene derivative.

71. The kit of claim 68, wherein said neutral capture probes are immobilized at the surface of a solid support.